The Incidence and Outcomes of Electronic Cigarette use in Pregnant Patients at Brody School of Medicine

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Abstract: This research study investigates the incidence and outcomes of e-cigarette use in pregnant patients at Brody School of Medicine through a retrospective analysis of medical records and a prospective survey. The need for this research is evidenced by the lack of knowledge in this topic area as seen through the duration of a concise literature review entailing the history, contents, FDA concerns, addictive properties, and the comparison of cigarettes versus e-cigarettes. Through data analysis, plausible correlations between the usage of e-cigarettes and pregnancy outcomes will be detailed. These findings will lead to greater awareness of complications due to e-cigarettes in the medical community which is especially important in the nicotine-dependent Eastern North Carolina area.

Keywords: nicotine, electronic cigarettes, pregnancy, outcomes, safety.

Introduction

Electronic cigarettes (e-cigarettes) are a form of electronic nicotine delivery systems that deliver nicotine in the form of aerosol (Grana, 2013). The e-cigarette is composed of a unit that contains e-liquid that can be comprised of nicotine, flavor additives, or a variety of other compounds (Food and Drug Administration, 2017). The worldwide use of e-cigarettes has steadily increased over the past decade due to rapid marketing and aggressive placement of these products (Yamin, 2010). With limited regulation of manufacturing, nicotine content, and knowledge about health safety, there are great concerns about the potential health consequences and the increased prevalence of e-cigarette, especially since they have not been proven to aid in smoking cessation (Grana, 2013). There is limited research about the impact these devices have on the health of users and the effects they have on other individuals in the users environment (Schripp et. Al., 2010). In recent findings, the Center for Disease Control (CDC) has reported that approximately half of the calls to poison centers are due to e-cigarette misuse by individuals twenty years and older (Chatham-Stephens et al., 2014). The lack of research has created an aura of uncertainty and controversy around a popular product in the general population. This popularity is indicated by the findings presented by researchers at the CDC that around 12.6% of adults in the United States have tried an e-cigarette at least once in their lifetime (CDC, 2015). Of this population, 21.6% were between the ages of 18-24 years old (CDC, 2015). Additionally, more than one-half of this total population were current or former conventional cigarette users (CDC, 2015).

Chinese pharmacist Hon Lik originally created the e-cigarette, and now there are more than 2500 brands sold worldwide (Yamin 2010). There is little or no data on efficacy of the e-

cigarette as a smoking cessation aid (Grana, 2013). The amount of nicotine delivered to the smoker varies greatly among the various brands of e-cigarettes (Cahn et al 2011). The American Food and Drug Administration (FDA) has only recently begun to regulate electronic cigarettes in 2016 under the new FDA Tobacco Rule (FDA, 2016).

The World Health Organization (WHO) has found that "tobacco is the single most preventable cause of death in the world today". According to the Center for Disease Control (CDC), tobacco use kills more than 1 million individuals in North and South America every year (CDC, 2013). Specifically, in North Carolina, in 2013, 21.8% of individuals above the age of 18 use cigarettes, and 5.8% of the same population use e-cigarettes (CDC 2013). This ranks North Carolina the 29th highest state in terms of tobacco usage (CDC 2013).

There is a clear trend of increased use e-cigarettes in the United States but the personal reasons for the use of e-cigarettes vary in the general population. A recent study completed through online surveys found that the most common reasons for e-cigarette use was personal smoking cessation and health concerns, health considerations for others exposed to second hand tobacco smoke, and the convenience of the product use (Huang et al 2016). This study on e-cigarette use, among others, generally conclude by stating that there is a need for scientific research to provide e-cigarette consumers with reliable and correct information regarding the effects that use of these devices have on consumers.

Since a large number of individuals in Eastern North Carolina (22%) are dependent on nicotine, it is important that research be done in the area to bring awareness to the issues that surround the lack of knowledge about the e-cigarette (CDC, 2013). While there exists a gap in knowledge concerning the topic of e-cigarettes, a greater gap exists in the current understanding

of the effect of e-cigarette use during pregnancy. For these reasons, it is important to delve deeper into the interrelations that may exist between pregnancy outcomes and e-cigarettes.

In the most recent report by the Surgeon General on the health consequences of smoking during pregnancy, over 100,000 cases of premature death in infants resulted from smoking (US Department of Health and Human Services, 2014). With respect to pregnancy and birth, women who smoke more than four conventional cigarettes per day during pregnancy have "small for date babies" and often deliver their infants before term (US Department of Health and Human Services, 2014). Nicotine exposure during pregnancy could lead to preterm birth, stillbirth, ectopic pregnancies, oral facial clefts, fetal growth restrictions, and negative effects on fetal brain development (US Department of Health and Human Services 2014). The safety of e-cigarettes has not been established for pregnant women (ACOG, 2011). The American College of Obstetricians and Gynecology (ACOG) has stressed preventative interventions that could reduce the prevalence of smoking during pregnancy. In fact, ACOG requires smoking cessation counseling for all pregnant women (ACOG, 2011). While screening for conventional cigarettes in routine, obstetricians and gynecologists may not specifically screen for the usage of electronic cigarettes during pregnancy. A recent study surveyed more than a thousand ACOG members and found that only 53% of this population screened their patients for the usage of any non-combustible tobacco products such as chewing tobacco and snuff (England, 2014).

Since vapors from e-cigarettes do not contain the combustion tars found in cigarette smoke, they are assumed to be less hazardous to the health of the user (Bullen, 2010). Vapors from e-cigarettes do not contain carbon monoxide which is an embryo toxic component of cigarette smoke (Bullen, 2010). There are lower amounts of nicotine absorption from e-cigarettes than conventional cigarettes presumably because the tars in tobacco smoke facilitate nicotine

uptake (Bullen, 2010). Animal studies have shown that nicotine can damage embryo development by reducing uterine blood flow (Holbrook, 2016). Large doses of nicotine are required to show an inhibition of fetal growth, but smoking does cause a transitory drop in blood flow to the placenta which could have adverse consequences during the embryonic phase of fetal development (Holbrook, 2016). People who are addicted to nicotine consume increased amounts of nicotine to return their blood levels to their "comfort zone" level. Nicotine-addicted cigarette smokers on arising raise their blood nicotine to their comfort range within five minutes of the onset of smoking their first morning cigarette (Holbrook, 2016). . This is often accompanied with light headiness or dizziness, which are symptoms of nicotine ganglionic blockade, and this level of nicotine exposure could reduce placental blood perfusion (Holbrook, 2016). In a study analyzing the effects of e-cigarette aerosol exposure in Xenopus laevis embryos and mammalian neural crest cells, it was found that e-cigarette exposure could have detrimental and adverse effects on craniofacial development (Kennedy et al., 2017). The potential vulnerability of the developing fetus to chemical insults from nicotine "over dosing" during early embryonic development, suggests research is needed to determine whether e-cigarettes are safe or unsafe for use in pregnancy.

This is becoming more important because of increased use of e-cigarettes in the past decade and the apparent lack of recording e-cigarettes use in pregnancy. Research on the health consequence of e-cigarette use in needed. This research project aims to determine the frequency of e-cigarette use, and the frequency that e-cigarette usage is recorded in patient records at the Brody School of Medicine Obstetrics and Gynecology Department's outpatient clinics. The low frequency of adverse pregnancy outcomes makes it important to document all factors that could

potentially contribute to an adverse outcome. With systematic recording of environmental factors the likelihood of detecting factors contributing to a low frequency events is increased.

The variables that are utilized in this study are APGAR score at 1 minute, APGAR score at 5 minutes, birthweight of the newborn (BWT), and mother's gestational age (GAGE). The APGAR score is a measurement that assesses the newborn's appearance, pulse, grimace responses, activity, and respiration. These five factors are each assessed on a scale of 0 to 2 and are combined to give a total perfect score of 10. This score is taken twice, once at the first minute after birth to assess how the newborn did during the birthing process, and once at five minutes after birth to assess how the newborn is doing outside the mother's womb. The birthweight (BWT) of the newborn is assessed in grams shortly after birth. The mother's gestational age is the measure of time in weeks that the pregnancy lasted. Typically, a healthy pregnancy will result in the mother having a gestational age of approximately 40 weeks.

Purpose of this Study

The purpose of this study is to examine the effect the usage of e-cigarettes on pregnancy outcomes. The study has two components. The first component is a prospective questionnaire to determine conventional and electronic cigarette use in patients at the East Carolina University obstetrics and gynecology clinic. The second component is a retrospective chart review examining birth outcomes of patients and recording whether electronic cigarette use is documented in patient charts.

Hypothesis

It is hypothesized that the use of e-cigarettes is recorded in the medical records of patients receiving care at the ECU Brody OBGYN Clinics. It is also hypothesized that the usage of

electronic cigarettes will shorten the term length of the pregnancy and reduce the birth weight of the newborn when studying non-diabetic women who do not engage in illicit drugs.

Methodology

We obtained approval for this research from the UMCIRB (University Medical Center Institutional Review Board, a board of with members from Vidant Medical center, East Carolina University and the lay public). To maintain patient confidentiality research data was stored in an OBGYN Departmental folder on the ECU Pirate-drive dedicated to the study. Only study team members had access to the files. Data was stripped of patient identifiers (HIPAA regulated information) prior to data analysis.

Prospective Survey Method

The incidence of e-cigarette usage in the ECU clinic population was estimated from patient responses to a prospective questionnaire administered by medical staff and doctors at Brody School of Medicine Clinics. Subjects were pregnant, non-diabetic women who were not using of illegal drugs. The questionnaire is shown in figure 1. The instructions allowed the subjects of participate on a volunteer basis in an anonymous fashion.

FIG 1. PROSPECTIVE QUESTIONNAIRE *Instructions: You are being invited to participate in a research study titled "The Effect of Electronic Cigarettes on Pregnancy Outcomes" being conducted by Ankita Mishra, a student at East Carolina University, and Dr. Charles Hodson, a professor at East Carolina University in the OB/Gyn department. The goal is to survey 100 individuals at the Brody Clinic. The survey will take approximately 10 minutes to complete. It is hoped that this information will help us understand the effects the usage of electronic cigarettes has on pregnancy outcomes and the frequency electronic cigarette use in pregnancy. The survey is anonymous, so please do not write your name on the survey form. Your participation in the research is voluntary. You may choose not to answer any or all questions, and you may stop at any time. There is no penalty for not taking part in this research study. Please call the principal investigator Charles Hodson at 252-744-2008 or Ankita Mishra at 919-397-1479 for any research related questions or the Office of Research Integrity & Compliance (ORIC) at 252-744-2914 for questions about your rights as a research participant. Please circle the choice that best suits your answer to the question. If the question does not apply to you, please circle "No", when you are finished place your survey in the survey collection box.*
1. Is this your first pregnancy?
2. What is your age range?
3. Have you smoked cigarettes during pregnancy?
4. Are you currently using cigarettes while pregnant?
5. Have you utilized electronic cigarettes while pregnant?
6. Are you currently using electronic cigarettes while pregnant?
7. What best describes your reasoning for using electronic cigarettes?
8. How often do you utilize electronic cigarettes?
9. Are you aware that there is the potential for trace amounts of nicotine to be present within electronic cigarettes?
10. Knowing the effects of nicotine on an unborn baby, does the presence of nicotine in electronic cigarettes influence you to stop smoking electronic cigarettes or refrain from using them in the future?

Retrospective Analysis Method

In the retrospective analysis component of this study, we retrospectively examined patient charts of pregnant women who were consulted with at the ECU Outpatient Clinics prior to their pregnancy and delivered at Vidant Medical Center. The charts of women who delivered at the Vidant Medical Center between 1/15/2015 and 10/5/2016 were examined. The data that was collected is indicated in figure 2 and included: infant birth weight (BWT), electronic cigarette usage, APGAR score at one minute (APGAR1), APGAR score at five minutes (APGAR5), and the gestational age of the mother (GAGE). Additionally, data was collected in regards to the women's smoking status (Current Smoker, Non-smoker, and Former Smoker). Participants in this study were pregnant women at the Brody School of Medicine Clinic who are not engaged in the use of illicit drugs.

FIG 2. RETROSPECTIVE ANALYSIS VARIABLES
Newborn Infant Birth Weight (BWT)
Mother's Usage of Electronic Cigarettes (ECIGUSE)
APGAR Score at One Minute (APGAR1)
APGAR Score at Five Minutes (APGAR5)
Gestational Age (GAGE)
Mother's Smoking Status During Pregnancy (Current, Non-, or Former Smoker)

Data and Results

Prospective Questionnaire Data and Results

The prospective component of the study, the electronic cigarette usage questionnaire, was given to new patients at the ECU Women's Physician's clinic. A total of 218 patients were anonymously surveyed. The results are summarized in Figure 3.

FIG 3. PROSPECTIVE ANALYSIS RESULTS	
What best describes your reasoning for using electronic cigarettes?	***Responses***
I do not use electronic cigarettes.	214
They are a safer alternative to smoking.	4
Are you aware that there is the potential for trace amounts of nicotine to be present within electronic cigarettes?	***Responses***
No	74
Yes	138
Knowing the effects of nicotine on an unborn baby, does the presence of nicotine in electronic cigarettes influence you to stop smoking electronic cigarettes or refrain from using them in the future?	***Responses***
No	20
Yes	57

Of these patients, four patients (n=4 answered the question "Do you currently use electronic cigarettes?" with a 'yes'. The patients who responded with a 'yes' when asked about e-cigarette use (n=4) were 18-25 years old (n=2) and 26-32 years old (n=2). Of the patients who responded 'yes' to e-cigarette use, four patients (n=4) answered that their reasoning for utilizing e-cigarettes during pregnancy is because they believed it was a safer alternative compared to smoking traditional cigarettes. A total of 138 respondents answered the question "Are you aware that there is nicotine present within electronic cigarettes?" with a 'yes' (n=138), and 74 respondents answered with 'no' (n=74). The majority of responses to this question was 'yes' for all age ranges identified in the survey. The majority of the respondents between the ages of 14-17 years old answered the question "Knowing that there is nicotine present in electronic cigarettes, would you still consider using electronic cigarettes?" with a 'yes' (n=57) and only twenty responded with a 'no' (n=20). The majority of respondents between the ages of 18-25 years old (n=78) responded to this question with a 'yes' (n=53) and fifteen responded by saying

'no' (n=15). When comparing these results to question #3 that asked respondents about previous cigarette use, the following was noted as pictured in Figures 4 and 5.

FIG 4. Knowing the effects of nicotine, will you use e-cigarettes?
Responses from Non-Smokers

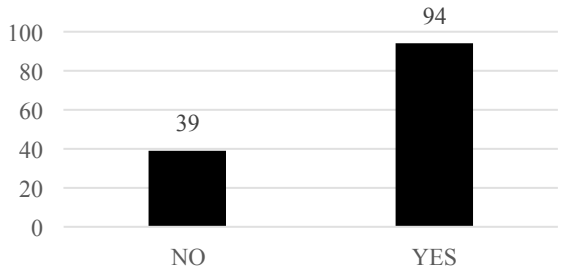

FIG 5. Knowing the effects of nicotine, will you use e-cigarettes?
Responses from Previous Cigarette Smokers

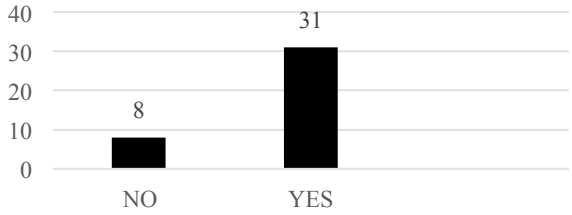

FIG. 7 RETROSPECTIVE RESULTS		
VARIABLES	**MEAN**	**STANDARD DEVIATION**
Smoking Status & Birth Weight	*Measured in Grams*	
Non-Smoker (n=166)	3283.157	661.7209
Smoker (n=32)	3143.906	624.2237
Smoking Status & Gestational Age	*Measured in Weeks*	
Non-Smoker (n=166)	38.58723	2.661134
Smoker (n=32)	38.68219	1.84769
Smoking Status & APGAR @ 1 min	*Measured in Minutes*	
Non-Smoker (n=166)	7.795181	1.642312
Smoker (n=32)	7.1875	2.038935
Smoking Status & APGAR @ 5 min	*Measured in Minutes*	
Non-Smoker (n=166)	8.626506	0.9106886
Smoker (n=32)	8.5625	0.7593503

Retrospective Analysis Data and Results

A retrospective analysis of patient medical records from the Obstetrician and Gynecology clinic at Brody School of Medicine from 1/15/2015 and 10/5/2016 resulted in a total of 212

medical records. Of these medical records, pregnancies that resulted in still born babies were removed and resulted in a total of 198 medical records that were utilized in this study. None of the records examined included notes of electronic cigarette usage during pregnancy. However, other variables such as birth weight, smoking status, gestational age, and APGAR scores displayed trends. The results are summarized in Figure 7.

According to the results, the average birthweight for a newborn who was born to a mother who does not smoke (nonsmoker, n=166) was between the range of 1500 grams and 4600 grams with a mean birthweight of 3283 grams. For mothers who did smoke (smoker, n=32), the birthweight for the newborn was between the range of 2000 and 4500 grams with a mean birthweight of 3143 grams.

Another variable that was assessed in the retrospective analysis was the mother's gestational age at delivery (GAGE). According to figures 6 and 7, the mean GAGE for nonsmokers is 38.58 weeks. The mean GAGE for smokers is 38.68 weeks. The mean APGAR1 score for newborns born to non-smokers was 8, and the mean APGAR1 score for newborns born to smokers was 8 as well. The mean APGAR5 score for newborns born to nonsmokers was 8.626, whereas the mean APGAR5 score for newborns born to smokers was 8.5625.

Of these findings, the trends between current smoking status compared to APGAR 1, AGAR 5, and birthweight of the newborn are significant.

The results from the 1-tail and 2-tail tests of variables in the retrospective analysis as they compare the smoking status are indicated in Figure 8.

FIG 8. Results from 1 and 2 Tail Test as compared to Smoking Status

VARIABLE	P-Value for 2-Tail Test	P-Value for 1-Tail Test
Birth Weight	0.16	0.004
Gestational Age at Delivery	0.07	0.018

APGAR score at 1 minute	0.17	0.003
APGAR score at 5 minutes	0.058	0.09

Of these values, the 1-tail tests indicate significance for the following variables when compared to smoking status: birth weight, gestational age, and APGAR score at 1 minute. Figures 12-14 illustrate the differences between smokers and nonsmokers when assessing birth weight and gestational age.

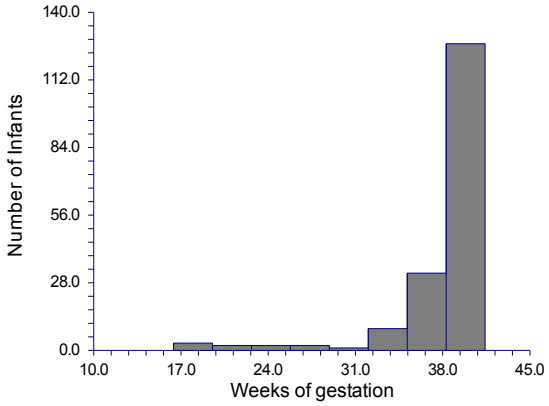

Fig 9. Gestational Age Distribution in Non-Smoker Population (n=166)

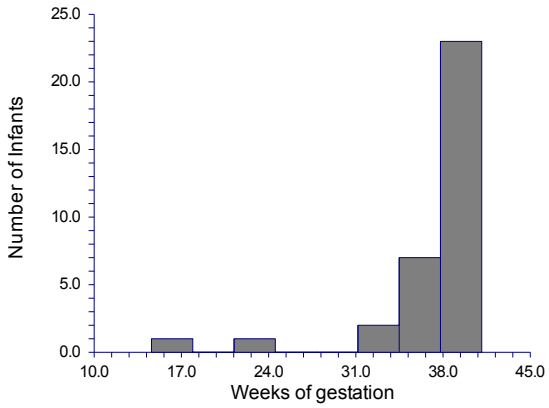

Fig 10. Gestational Age Distribution in Smoker Population (n=32)

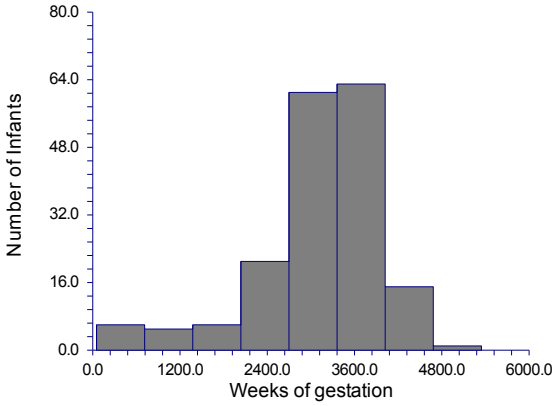

Fig 11. Birth Weight Distribution in Non-Smoker Population (n=166)

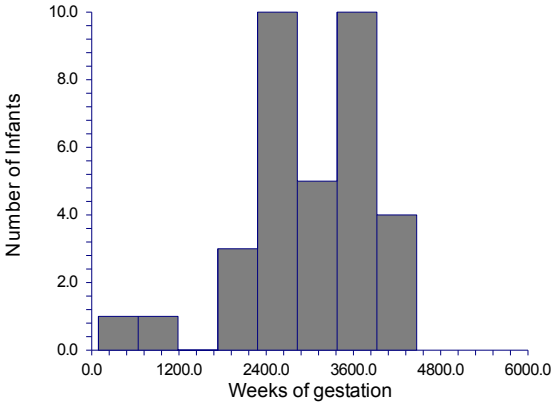

Fig 12. Birth Weight Distribution in Non-Smoker Population (n=166)

According to figure 9, 3.6% of the non-smoker population delivered newborns before 30 weeks. In comparison, figure 10 indicates that 12.5% of the smoker population delivered newborns before 30 weeks. Figure 11 indicates that 9% of the non-smoker population delivered newborns that had a birth weight below 2400 grams. In comparison, figure 12 indicates that 15.6% of the smoker population delivered newborns that had a birth weight below 2400 grams.

Discussion

The hypothesis that was established prior to the study was that e-cigarette usage would be recorded in the medical records of patients receiving care at the ECU Brody OB/GYN Clinics. Additionally, it was hypothesized that e-cigarette usage would negatively impact birth outcomes including gestational age, APGAR score at 1 and 5 minutes, and birthweight. The results indicate that e-cigarette usage is not recorded in the medical records of patients receiving care at the ECU Brody OB/GYN Clinics and in the Vidant Medical Center medical records. No e-cigarette users were identified in the retrospective analysis portion of this study between 1/15/2015 and 10/5/2016. However, conventional smoking status was noted in the medical records of patients receiving care at the ECU Brody OB/GYN Clinics. For this reason, the study was shifted towards looking at the birth outcomes as it relates to conventional cigarette smoking status. The variables that were assessed and identified from the medical records in the retrospective analysis were: APGAR score at 1 minute, APGAR score at 5 minute, gestational age, newborn birthweight, and mother's smoking status. Of these variables, the data suggests that current conventional cigarette smoking status has an effect on APGAR score at 1 minute, gestational age, and birthweight.

It is important to note that from the total population that was utilized in the retrospective portion of this study (n=198), a total of 166 patients were non-smokers (n=166) and only 32 were

smokers (n=32). This means that there was 5x as many pregnant women who were identified as non-smokers used in this study as compared to smokers. The results would lead to greater significance if the population of smokers and non-smokers were more even in number. Typically, in studies within the field of Obstetrics and Gynecology, outcomes such as gestational age, birthweight, and APGAR score are not evenly distributed.

The results from the prospective study indicated that, while no e-cigarettes users were found in the retrospective analysis of the medical records, four survey participants answered with a 'yes' to e-cigarette use. This means that medical professionals should be more cognizant of inquiring about e-cigarette use by their patients whether or not it is a question that the medical record system asks for. Additionally, the data suggests that of the pregnant patients that were surveyed, e-cigarette use was more common in younger patients. The most common reason for utilizing e-cigarettes was due to respondents seeing it is a 'safer' alternative to smoking conventional cigarettes. The data implies that most patients surveyed do not realize that trace amounts of nicotine are present within e-cigarettes, but after completing the survey they would not be likely to engage in e-cigarette use.

This research study makes evident the need for further study and investigation in the links between e-cigarette use and pregnancy outcomes. It is important that medical professionals not only inquire about e-cigarette use in their patients, but also make patients aware of the potential harmful effects when engaging in e-cigarette use.

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